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Highly Diastereoselective Friedel–Crafts Reaction of Furans with 8-Phenylmenthyl Glyoxylate

Piotr Kwiatkowski,[†] Jakub Majer,[†] Wojciech Chaładaj,[†] and Janusz Jurczak*[,†,‡]

Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warsaw, Poland, and Department of Chemistry, Warsaw University, 02-093 Warsaw, Poland

jurczak@icho.edu.pl

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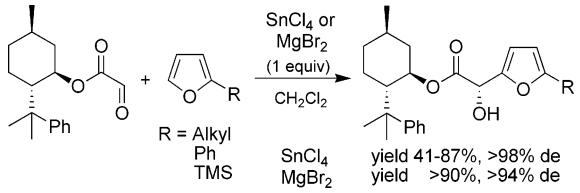
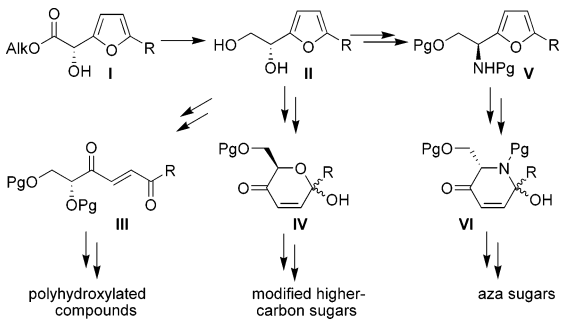
ABSTRACT



The Friedel–Crafts reaction of (1*R*)-8-phenylmenthyl glyoxylate with variously substituted furans was found to be efficiently promoted by $SnCl_4$ or magnesium salts with high diastereoselectivities. $MgBr_2$ performs especially well under simple, undemanding conditions, giving both high yields and high diastereoselectivities (>90%). The reaction afforded chiral substituted furan-2-yl-hydroxyacetic acid esters, compounds of potentially high synthetic interest.

The optically active furanyl α-hydroxyacetic acid esters (**I**) and products of their reductions, i.e., 1,2-diols of type **II**, are of great synthetic importance (Scheme 1).[1] The latter alcohols, as a result of the presence of the furanyl moiety in their structure, can be easily converted under oxidizing conditions to very interesting linear (**III**)[2] as well as cyclic products (**IV**)[3,4] (Scheme 1). Such an approach was utilized, e.g., for the synthesis of multifunctional chain compounds[2] or higher-carbon sugars.[3] Diols bearing aryl substituents in position 5 were applied in the synthesis of spiroketal moiety of papulacandin D.[4a] They can be transformed also to amino alcohol derivatives of type **V**,[5] leading under oxidizing conditions to dihydropyridones **VI** useful in the synthesis of aza sugars.[5,6]

Scheme 1. Application of Furanyl α-Hydroxyacetic Derivatives or Corresponding Diols in the Synthesis



The literature reports only a few methods for the synthesis of optically pure 2-furylcarbinols of type **I**. The most efficient methods rely on the enzymatic resolution of racemic mixtures using a lipase[7] or on kinetic resolution using the Sharpless

[†] Polish Academy of Sciences.
[‡] Warsaw University.

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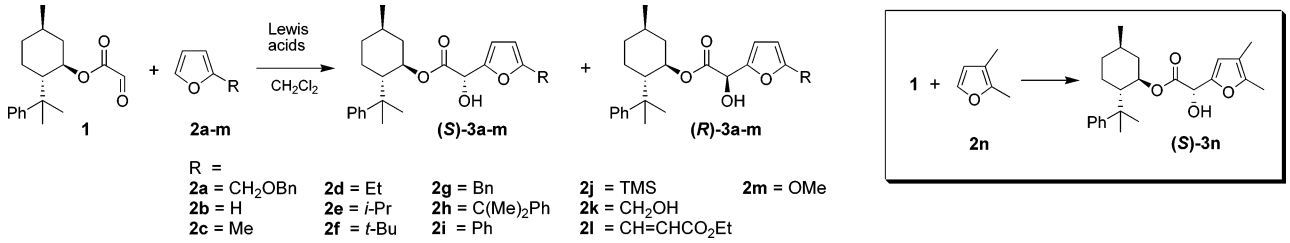
Scheme 2. Friedel−Crafts Reaction of Variously Substituted Furans with the Glyoxylate **1**



reagent.[8] The appropriate 1,2-diols of type **II** can be obtained via Sharpless asymmetric dihydroxylation of 5-substituted vinylfurans,[4] and the simplest one of them, the unsubstituted diol (R = H) can be obtained from the sugar derivatives (e.g., D-glucal).[9]

The most attractive methods appear to be direct ones employing a synthesis from the corresponding furans and aldehydes. Such an approach can be performed in two ways: by addition of lithiated furans to the carbonyl group or by the Lewis acid catalyzed Friedel−Crafts reaction. Until now, there was no effective diastereoselective[10] or enantioselective[11,12] synthetic method for furan derivatives of type **I** based on the latter approach. However, there are known examples of efficient diastereoselective[13] and enantioselective[11,14,15] Friedel−Crafts reactions of carbonyl compounds with other aromatic derivatives.

Following our attempts to use chiral metallosalen complexes,[12] we decided on more detailed investigation of the possibility of using chiral derivatives of glyoxylic acid. Until now, menthyl glyoxylate has been tried for this reaction,[10,12b] but as one could expect, it gave low asymmetric inductions. Because of that, we used its 8-phenylmenthyl derivative **1**[16] (Scheme 2). Glyoxylate **1** had been originally applied to the nucleophilic additions of organometallic species (e.g., Grignard reagents) and ene reaction by Whitesell.[17,18] In the literature, there are also examples of application of the glyoxylate **1**, e.g., in Diels−Alder,[19] Morita−Baylis−Hillman,[20] nitroaldol,[21] allyl,[22] and vinyl substitution reactions.[23] Besides, it was also used by Bigi et al. in the Friedel−Crafts reaction, but only with phenols[13a,b] and O-protected phenols[13c] in the presence of $TiCl_4$ or $SnCl_4$, leading to 2- and 4-hydroxymandelic esters, respectively with high stereoselectivities. According to the literature, these Lewis acids are also the most efficient in other types of reactions with glyoxylate **1** (usually, 1 equiv is needed).[18−23]

In this paper, we describe a highly diastereoselective Friedel−Crafts reaction of (1*R*)-8-phenylmenthyl glyoxylate (**1**) with variously substituted furans **2a**−**n** (Scheme 2, 14 examples). In our study, $SnCl_4$ gave higher diastereoselectivities (>98% de) compared to those of $TiCl_4$. We have studied extensively the reaction of **1** with benzyl furfuryl ether (**2a**), which was originally used by Achmatowicz in the total synthesis of racemic uloses.[3] This reaction, in the presence of a stoichiometric amount of $SnCl_4$, proceeds to give good yield and very high diastereoselectivity (Table 1, entry 1). We have tested also several other furan systems in this reaction, e.g., furan itself, and 2-methyl-, benzyl-, and phenyl-substituted furans, and each time we have observed also a very high diastereoselectivity (>99% de, Table 1, entries 2−6). This procedure can be successfully applied even to 2-trimethylsilylfuran (**2j**), unprotected furfuryl alcohol (**2k**), and furans bearing an electron-withdrawing group (**2l**)

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Table 1. Friedel−Crafts Reaction of Furans with **1** Promoted by $SnCl_4$[a]

			product		
entry	furan	time (h)	no.	yield (%)[b]	de (%)[c]
1	**2a**	5	**3a**	87	>99
2	**2b**	2	**3b**	56	>99 (*S*)
3	**2c**	2	**3c**	41	>99 (*S*)
4	**2g**	2	**3g**	79	>99
5	**2h**	2	**3h**	50	>99
6	**2i**	4	**3i**	87	>99
7	**2j**	2	**3j**	45	>99
8	**2k**	2	**3k**	60	>99
9	**2l**	5	**3l**	63	98

[a] The reactions were carried out using 0.5 mmol of the glyoxylate **1** in 3.0 mL of CH_2Cl_2, 1 equiv of $SnCl_4$, and 1.5 equiv of furan at −78 °C. [b] Isolated yield. [c] Diastereomeric excess determined by HPLC and ^1H NMR.

(entries 7−9). However, the yields were substantially lower (about 50%) in many cases, probably because of partial decomposition of the furan derivatives.

Therefore, we decided to search for milder Lewis acids that would allow these reactions to be conducted efficiently and highly stereoselectively, catalysts that would be less toxic than $SnCl_4$, require less demanding conditions, and avoid the necessity of using dry solvents. We focused our attention, inter alia, on zinc and magnesium salts. Zinc bromide was used by our research group in the reactions with chiral derivatives of glyoxylic acids, often giving high stereoselectivities, e.g., in the allylation reaction.[22b] As a model furan substrate, benzyl furfuryl ether (**2a**) was used, but the reaction using zinc bromide gave a moderate diastereomeric excess (~65% de, Table 2, entry 1). Replacing **2a** with silvan (**2c**)

Table 2. Screening of Lewis Acids in the Reaction of **1** with **2a**[a]

entry	Lewis acid	time (h)	yield (%)[b]	de (%)[c]
1	$ZnBr_2$	4	60	65
2	$MgCl_2$	24	61	85
3	$MgBr_2$, anhydrous	2	96	89
4	$MgBr_2 \cdot Et_2O$	5	93	86
5	$MgBr_2 \cdot 0.5H_2O$	5	97	90
6	$MgBr_2 \cdot 1.5H_2O$	24	58	91
7	$MgBr_2$ (20 mol %)	72	39	65

[a] The reactions were carried out using 0.5 mmol of **1** in 2.5 mL of CH_2Cl_2, 1 equiv of Lewis acid (entries 1−6), and 1.5 equiv of **2a** at 20 °C. [b] Isolated yield. [c] Determined by HPLC and ^1H NMR.

gave somewhat better results (80% de). These results were utterly unsatisfactory because most of the products of these reactions were oils.

We found magnesium chloride to be a stereochemically more effective (85% de) Lewis acid catalyst for the reaction of **2a** with **1** (Table 2, entry 2). However, the yield was rather moderate, and the reaction required prolonged time. Because of that, we decided to try other easily available magnesium salts. The best results were obtained for magnesium bromide, which appeared to be much more active than $MgCl_2$, requiring only 2 h at room temperature to complete the reaction (entry 3) with a slight increase of the asymmetric induction. Magnesium bromide etherate can be also used successfully (entry 4).

We have also investigated the effect of the presence of water and the possibility of using catalytical amounts of $MgBr_2$. In the case of using anhydrous $MgBr_2$, trace amounts of byproducts are observed. Addition of water in an amount of ca. 0.5−0.7 equiv with respect to the magnesium salt had practically no influence on the asymmetric induction nor the yield (entry 5), but it did help to eliminate byproducts.[24] In order to obtain such hydrated magnesium bromide, it is enough to keep anhydrous $MgBr_2$ or its etherate in an open flask for ca. 12 h.[25] The presence of water in an amount slightly exceeding 1 equiv slows down the reaction rate substantially, but the selectivity is still high (entry 6). In the case of using $MgBr_2 \cdot 6H_2O$, the reaction practically does not occur.

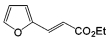
In conclusion, $MgBr_2$ containing less than 1 equiv of water is an efficient promoter of this reaction. The reaction in the presence of $MgBr_2$ is not reversible,[26] and the diastereomeric ratio is practically constant during the reaction.[27] Unfortunately, in order to obtain high diastereomeric excess, one has to use stoichiometric amounts of the magnesium salts, probably because of the strong affinity of magnesium to the product. In the case of using catalytical amounts of $MgBr_2$, a substantial drop in the selectivity as well as low reaction yield are observed (entry 7)

The results of the model reaction using a stoichiometric amount of $MgBr_2$, although inferior to the diastereoselectivities using $SnCl_4$, demonstrate that this reaction can be easily conducted at room temperature without a need for using dry solvents and reagents with very high yield. Prompted by very good results in the reaction of 8-phenylmenthyl glyoxylate (**1**) with benzyl furfuryl ether (**2a**) in the presence of the magnesium salts, we decided to investigate the possibility of using other furans for the reaction in the presence of conditioned $MgBr_2$, containing ca. 0.5 equiv of water (Table 3). Because of the very attractive properties of $MgCl_2$,[28] we also studied systematically the possibility of using it in the reactions in question.

Alkyl derivatives of furan are more reactive than benzyl furfuryl ether (**2a**). Because of that, $MgCl_2$ catalyzes these reactions, giving very good yields (usually >90% after 24 h). However, in many instances, the obtained inductions do not exceed 90%, usually being about 85%, as in the case of the furans **2a** (Table 2, entry 2) as well as **2c** (Table 3, entry 3). The rare exceptions are the furans substituted with benzyl

(24) The TLC chromatogram of the reaction mixture is very neat.
(25) The weight of anhydrous $MgBr_2$ was steadily rising.
(26) $MgBr_2$ (1 equiv) added to a mixture of product **3a** (65% de) causes no change in diastereomeric ratio after 24 h.
(27) Diastereomeric excess of **3a** in the reaction promoted by 1 equiv of $MgBr_2$ was practically constant after 5, 10, 15, 30 min, 1 h and 3 h.
(28) Despite low activity, from the application viewpoint $MgCl_2$ seems to be an ideal promoter-Lewis acid, because of minimum toxicity, low cost, and ease of handling.

Table 3. Application of Various Furans (**2a**−**n**) in the Magnesium-Promoted Reaction with **1**: Scope and Limitation[a]

entry	furan	Lewis acid (1 equiv)	time (h)	product no.	yield (%)[b]	de (%)[c]
1		$MgCl_2$	18	**3b**	72	88 (*S*)
2		$MgBr_2$	3	**3b**	97	90 (*S*)
3		$MgCl_2$	24	**3c**	98	86 (*S*)
4		$MgBr_2$	2	**3c**	94	94 (*S*)
5		$MgBr_2$	3	**3n**	97	94 (*S*)
6		$MgBr_2$	3	**3d**	97	95
7		$MgBr_2$	3	**3e**	91	95
8		$MgBr_2$	3	**3f**	97	97
9		$MgCl_2$	24	**3g**	98	96
10		$MgBr_2$	2	**3g**	98	96
11		$MgBr_2$	2	**3h**	96	97
12		$MgCl_2$	45	**3i**	97	98
13		$MgBr_2$	3	**3i**	98	99
14		$MgCl_2$	24	**3j**	72	92
15		$MgBr_2$	3	**3j**	98	98
16		$MgBr_2$	5	**3k**	85	79
17		$MgBr_2$	24	**3l**	70	83
18[d]		$MgBr_2$	2	**3m**	95	84

[a] The reactions were carried out using 0.5 mmol of **1** in 2.5 mL of CH_2Cl_2, 1 equiv of magnesium salt, and 1.5 equiv of furan at 20 °C. [b] Isolated yield. [c] Determined by HPLC and ^1H NMR. [d] The reaction was carried out at −5 °C.

(**2g**), phenyl (**2i**), and trimethylsilyl (**2j**), where the asymmetric inductions in the presence of $MgCl_2$ exceed 90% de (Table 3, entries 9, 12, and 14, respectively). In the other cases, much better results are obtained using the more active $MgBr_2$. Actually, all alkyl derivatives of furan **2c**−**h** and **2n**, and even phenylfuran (**2i**) and trimethylsilylfuran (**2j**), in the presence of $MgBr_2$, make it possible obtain the products having very high diastereomeric excesses (94−99%). Although the stereoselectivities obtained for $MgBr_2$ are slightly lower compared to those with $SnCl_4$, the reaction gives clearly better yields (>90% in not more than 3 h) and is much easier to carry out.

As shown in Table 3, the synthesis is highly selective (usually >90% de). The differences are very small for the furans substituted at the 2-position with alkyls of various spatial requirements (**2c**−**h**), aryl (**2i**), trimethylsilyl (**2j**), and even 2,3-disubstituted furans (**2n**). Lower selectivities (~80% de) are obtained only for furans **2k**−**m**.

Out of the 14 novel products, two compounds (**3b**, **3c**) have been subjected to determination of the absolute configuration by chemical correlations,[9,12b] and the configuration of **3n** has been directly determined using X-ray crystallographic analysis (Figure 1). In all the cases, a product of (*S*)-configuration was obtained from (1*R*,2*S*,5*R*)-8-phenylmenthyl glyoxylate (**1**). Such a direction of induction is in accordance with the literature data concerning other additions and cycloadditions to **1**.[17−23] One can assume with a high likelihood that the induction direction is identical for all of the investigated reactions of furans with aldehyde **1** in the presence of $SnCl_4$ or $MgBr_2$.

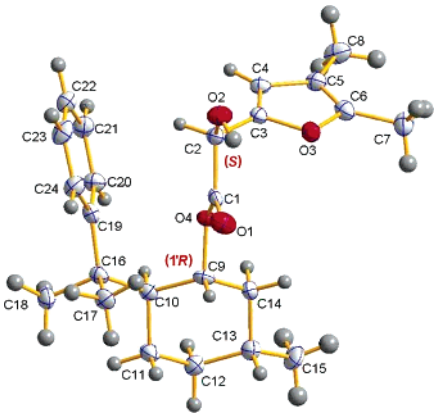


Figure 1. X-ray crystal structure of compound (*S*)-**3n**

In conclusion, we have developed a general, efficient, and undemanding method for the diastereoselective synthesis of chiral variously 5-substituted furan-2-yl-hydroxyacetic acid esters, compounds of significant synthetic interest, with high optical purity (de usually over 90% up to >99%). Although $SnCl_4$ allows for obtaining very high diastereoselectivities, the magnesium salts seem to be more attractive since they give better yields. The reaction is clearly and reproducible promoted by inexpensive and low-toxicity $MgBr_2$ and $MgCl_2$ at room temperature without the need of using dry solvents and inert atmosphere. According to our knowledge, this is the first example of a highly stereoselective reaction of furans with glyoxylates.

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Supporting Information Available: Experimental procedures and analytical data for all new compounds (**3a**−**n**) with reprints of NMR spectra and X-ray information for (*S*)-**3n** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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